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## **Shared neural basis of social and non-social reward deficits in chronic cocaine users**

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# Shared neural basis of social and non-social reward deficits in chronic cocaine users

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## Abstract

Changed reward functions have been proposed as a core feature of stimulant addiction, typically observed as reduced neural responses to non-drug-related rewards. However, it was unclear yet how specific this deficit is for different types of non-drug rewards arising from social and non-social reinforcements. We used functional neuroimaging in cocaine users to investigate explicit social reward as modeled by agreement of music preferences with music experts. In addition, we investigated non-social reward as modeled by winning desired music pieces. The study included 17 chronic cocaine users and 17 matched stimulant-naïve healthy controls. Cocaine users, compared with controls, showed blunted neural responses to both social and non-social reward. Activation differences were located in the ventromedial prefrontal cortex overlapping for both reward types and, thus, suggesting a non-specific deficit in the processing of non-drug rewards. Interestingly, in the posterior lateral orbitofrontal cortex, social reward responses of cocaine users decreased with the degree to which they were influenced by social feedback from the experts, a response pattern that was opposite to that observed in healthy controls. The present results suggest that cocaine users likely suffer from a generalized impairment in value representation as well as from an aberrant processing of social feedback.

**Key words:** fMRI; social conformity; social cognition; dopamine; drug dependence; OFC

## Introduction

Stimulant addiction is a prevalent disease with wide-ranging adverse consequences for individuals, families and societies (Degenhardt and Hall, 2012). It is characterized by impulsive and compulsive taking of substances acting at monoamine transporters and modulating the frontostriatal reward system, which guides adaptive behavior (Ersche *et al.*, 2013). It has been consistently shown that cocaine users display decreased gray matter volume of the orbitofrontal cortex (OFC), ventromedial

prefrontal cortex (vmPFC) and insula (Franklin *et al.*, 2002; Ersche *et al.*, 2011). In addition, a study using positron emission tomography revealed lower glucose metabolism in the OFC of cocaine users, which was correlated with lower dopamine D2 receptor density in the striatum of this group (Volkow *et al.*, 1993). Particularly ventromedial and orbitofrontal cortical regions have been associated with abnormal processing of monetary rewards in individuals with stimulant addiction (Goldstein *et al.*, 2007a,b; Jia *et al.*, 2011; Patel *et al.*, 2013). However, it is

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currently unclear whether the same ventromedial and orbitofrontal areas process rewards irrespective of reward type or whether reward signals are specific for reward type. Supporting evidence for both views has been reported (e.g., Howard *et al.*, 2015). For example, the signals reflecting social reward (Klucharev *et al.*, 2009; Burke *et al.*, 2010; Campbell-Meiklejohn *et al.*, 2010), such as approval, positive social feedback and reciprocity, may co-occur with (Bhanji and Delgado, 2014; Morelli *et al.*, 2015), or be at least partly distinct from (Sescousse *et al.*, 2013b; Seid-Fatemi and Tobler, 2015), the signals reflecting non-social reward, such as food or money. This issue is clinically relevant because another form of addiction, that is pathological gambling, has been characterized by differential neural sensitivity to social and non-social reward types (Sescousse *et al.*, 2013a). Yet, this important question is entirely unaddressed in individuals with stimulant addiction, although it was recently demonstrated that cocaine users display a variety of deficits in social cognition and social interaction (Hulka *et al.*, 2013, 2014; Preller *et al.*, 2014 a,b).

Stimulant addiction is associated with enhanced drug reward signals and reduced non-drug reward signals, at least when these rewards are non-social (Goldstein *et al.*, 2007a,b; Jia *et al.*, 2011; Patel *et al.*, 2013). One single study suggests blunted processing of implicit forms of social reward, such as sharing attention on an object with others (joint attention), in cocaine users (Preller *et al.*, 2014a). However, nothing is known yet about processing of more explicit social reward in stimulant addiction. Moreover, social and non-social reward have not been directly compared in stimulant addiction and it therefore remains an open question whether the blunting of non-drug reward signals co-occurs for social and non-social rewards. Thus, here we asked whether regular cocaine users show blunted responses to explicit social and non-social types of non-drug-related reward. Specifically, we focused on the vmPFC and the OFC, regions commonly implicated in social and non-social reward processing in healthy human subjects (Sescousse *et al.*, 2013b; Morelli *et al.*, 2015).

## Methods and Materials

### Participant recruitment and selection

Participants of the present study were selected from the Zurich Cocaine Cognition Study (ZuCo<sup>2</sup>St) sample and largely overlapped with those of a previous study (Preller *et al.*, 2014a). The participants of the ZuCo<sup>2</sup>St had been recruited by means of advertisements in local newspapers (cocaine users and controls), drug prevention and treatment centers (cocaine users), psychiatric hospitals (cocaine users), online media (cocaine users and controls) and by word of mouth (Preller *et al.*, 2013; Vonmoos *et al.*, 2013). All participants (Table 1) were aged between 18 and 60 years, had sufficient German language skills, had normal or corrected to normal vision, were right-handed as confirmed by the Edinburgh Handedness Questionnaire (Oldfield, 1971) and fulfilled magnetic resonance imaging (MRI) safety criteria. A Structured Clinical Interview for axis-I DSM-IV Disorders was carried out by a trained psychologist. Drug use data were collected by means of the Interview for Psychotropic Drug Consumption (Quednow *et al.*, 2004). The brief version of the Cocaine Craving Questionnaire (Tiffany *et al.*, 1993) was applied to assess current cocaine craving. Smoking habits were captured with the Fagerström Test of Nicotine Dependence (FTND) (Heatherton *et al.*, 1991). The Mehrfachwahl-Wortschatz-Intelligenztest (Lehrl, 1999), a standardized German vocabulary test, was carried out for the estimation of premorbid verbal IQ.

The Beck Depression Inventory (BDI) was used to assess current symptoms of depression (Beck *et al.*, 1961).

Specific inclusion criteria for the cocaine group were cocaine use of at least 1 g per month, cocaine as the preferentially used illegal drug, and a current abstinence duration of no longer than 6 months. Exclusion criteria for cocaine users were previous or present axis-I DSM-IV adult psychiatric disorders other than cocaine, nicotine and alcohol abuse/dependence, history of depression, and attention-deficit/hyperactivity disorder (because of the high comorbidity with cocaine use). Moreover, intake of opioids and a polytoxic drug-use pattern according to DSM-IV was not permitted and controlled by toxicological hair tests (see below). Exclusion criteria for control subjects were any axis-I DSM-IV psychiatric disorder with exception of nicotine dependence, and regular illegal drug use (lifetime use <15 occasions) with exception of occasional cannabis use. For both groups, exclusion criteria were severe medical diseases known to affect the central nervous system (CNS), head injury or neurological disorders, family history of schizophrenia or bipolar disorder and use of prescription drugs affecting the CNS. Participants were asked to abstain from illegal substances for a minimum of 3 days and from alcohol for at least 24 h. Self-reports were controlled by urine screenings and 6-month-hair tests (for further technical details see Preller *et al.*, 2013; Vonmoos *et al.*, 2013).

The initial sample population of this study consisted of 20 cocaine users and 24 controls. Completion of the task was not possible for two cocaine users and one control because of technical problems. One cocaine user and three controls were excluded due to excessive head movement during scanning (>3 mm). Further three controls were excluded because of matching reasons (age, verbal IQ, education and smoking); therefore, data of 17 controls and 17 cocaine users were finally analyzed. The studies were approved by the Cantonal Ethics Committee of Zurich. All participants provided written informed-consent statements in accordance with the declaration of Helsinki and were compensated for their participation.

### Procedure and task

**Pre-scanning.** Several days before the test day, subjects submitted a list of 20 songs that could be purchased from an online music store. Each song should be desired by the subjects but not owned yet. On arrival to the MR center, subjects had their photo taken and rated each of their 20 songs for desirability on a scale from 1 (I do not want this song) to 10 (I really want this song). Subjects also looked at pictures of two virtual music experts and read descriptions of them, which were derived from Campbell-Meiklejohn *et al.* (2010) and translated into German. Descriptions were created to communicate a degree of expertise across a broad range of popular music tastes. Subjects were asked to rate each reviewer from 1 (not at all) to 7 (very much) for how much the person could be trusted to pick music that the subject would like and informed that the two experts had listened to the 20 songs and provided reviews for each. Reviews were preferences between each of the 20 subject-provided songs and an alternative song, provided by the experimenter. Each subject-provided song was reviewed six times (relative to six different alternative songs). Subjects received instructions for the task and answered a series of questions to confirm that their task was understood.

**Task and timing.** The task was programmed and run using Presentation v.12 (Neurobehavioural Systems). Visual displays were presented with video goggles (Resonance Technology, USA). Responses (from the right hand) were collected using a

**Table 1.** Demographic data and drug use (means and standard deviations in parenthesis)

	Stimulant-naive controls (n = 17)	Chronic cocaine users (n = 17)
Male/female participants	12/5	13/4
Age, y	34.5 (8.8)	33.0 (8.6)
Education, y	11.1 (1.7)	11.1 (1.5)
Verbal intelligence quotient	108.2 (10.7)	104.5 (10.4)
Smoker/non-smoker, n	10/7	11/6
FTND sum score, 0–10*	1.9 (2.57)	4.6 (3.6)
BDI sum score, 0–63	3.0 (2.09)	7.2 (8.7)
Cocaine		
Times per week	–	0.8 (0.8)
Grams/week	–	1.0 (1.2)
Years of use	–	8.4 (5.3)
Maximum dose during 24 h	–	3.5 (2.2)
Last consumption (days)	–	15.3 (16.6)
Cumulative dose (grams)	–	693.7 (815.0)
Craving for cocaine, 0–70	–	20.4 (13.0)
Hair sample (pg/mg)		
Cocaine	–	9253.8 (16859.7)
Benzoylcegonine	–	1672.9 (2729.9)
Ethylcocaine	–	359.1 (604.8)
Norcocaine	–	224.0 (455.8)
MDMA		
Tablets/week	–	0.1 (0.2)
Years of use	–	2.4 (3.3)
Last consumption (days)	–	100.4 (n = 1)
Cumulative dose (tablets)	0.06 (0.24)	16.6 (24.1)
Hair sample (pg/mg)	–	150.8 (494.9)
Cannabis		
Grams/week	0.01 (0.0)	0.6 (1.5)
Years of use	1.6 (2.5)	9.8 (9.6)
Last consumption (days)	132.7 (117.7) (n = 4)	12.5 (20.4) (n = 7)
Cumulative dose (grams)	56.1 (111.0)	510.7 (1050.8)
Amphetamine		
Grams/week	–	0.04 (0.1)
Years of use	–	1.9 (3.8)
Last consumption (days)	–	60.0 (31.6) (n = 3)
Cumulative dose (grams)	–	15.1 (31.8)
Hair sample (pg/mg)	–	14.1 (55.7)
Alcohol		
Grams/week	95.8 (141.8)	259.6 (558.6)
Years of use	13.9 (10.1)	14.4 (8.9)
Nicotine		
Cigarettes per day (CPD)	4.4 (7.6)	10.8 (11.7)
Years of use	7.7 (8.6)	10.0 (9.5)

Consumption per week, duration of use and cumulative dose are averaged within the total group. Last consumption is averaged only for individuals who used the drug in the last 6 months. In this case, sample size (n) is shown. BDI, Beck Depression Inventory; FTND, Fagerström Test of Nicotine Dependence (\*measured in smokers only); MDMA, 3,4-methylenedioxy-N-methylamphetamine.

two-button response box. Each trial (Figure 1) began with a choice for the subject. We presented subjects with two songs at the top of the screen. One was a song that the subject provided. The other was an alternative, provided by the experimenter. The alternative was a Canadian or Scandinavian pop song, which was real, but unknown to the subject (confirmed after the scan session). Songs were randomly displayed on the left and right side of the screen with the constraint that subject-provided songs appeared equally often on left and right sides. Pictures of the experts were arranged vertically down the center of the display. A picture of the subject appeared at the bottom

of the screen, beneath the expert pictures. The words 'I prefer' were placed under each photo. The subject's task was to move their own picture beneath the song they desired the most. Subjects pressed the left button to move their picture left, or the right button to move it right. A scrambled picture of the subject was placed under the song they did not choose. Subjects were told that the song that they chose had a slightly (<5%) higher chance of being chosen for a token at the end of the trial to provide motivation to pick their real preference. Each song actually had a 50% chance of being chosen. Subjects knew that the songs with the most tokens at the end of the task were to be purchased for them and placed on a CD. There was a time limit of 2 s to make a choice. If no choice was made, a large 'X' appeared on the screen for the remainder of the trial. After making their choice, subjects learned about the expert's opinions. The pictures of each expert were moved under their respective preference. Scrambled pictures of the experts were placed under songs they did not choose. Experts could both prefer the subject-provided song, both prefer the alternative or both disagree with each other. This phase is termed the review outcome and gives rise to social reward in the case of agreement with the subject. Next, the songs alternately changed color between green and white (every 50 ms, for 1 s). Finally, a song was chosen for a token and appeared at the bottom of the screen. This phase was the object outcome and gave rise to non-social reward in the case of token assignment to the subject-preferred song. Review outcomes were completely independent from object outcomes. During instruction, subjects confirmed that expert choices did not predict which song token would be received. The order of trials was optimized to provide maximum efficiency for detection of Blood Oxygenation Level Dependent (BOLD) activity related, independently, to different review and object outcomes. For these purposes, it was not possible to use real expert reviews, and confederate reviews were used in their place. As a result, trials could be placed close together in time with a brief minimum of 3 s between each modeled event, reducing subject time in the scanner but still controlling for non-linearities of the BOLD signal. Decisions appeared at time 0 of each trial. Review outcomes appeared at 3 s, and songs began to flash at 4 s. Object outcomes were presented at 5 s and remained on display for 2 s. A fixation cross was displayed for 2 s between each trial.

In total, there were 140 trials in six conditions the experiment (Figure 1). Four of the conditions included 28 trials (RsS, RsA, RaS and RaA), whereas two conditions were presented 14 times each (RsSplitS and RsSplitA). Only trials in which subjects chose the same song they had provided a week prior were included in the analysis. Trials were excluded in which no response occurred. Because of these criteria, a mean of 11.1% of trials per subject had to be excluded (range of mean excluded trials across six conditions: 10.3–12.8%). Importantly, no participant was included who made an error in more than half of the trials in each condition.

**Post-scanning.** After completing the task, subjects rated each of their 20 songs for desirability for a second time. Subjects were also asked whether they had learned more about the reviewers or more about the songs. The 10 songs for which the subject had the most tokens (from the object outcome of the task) were purchased for the subject and handed over on CD or memory stick.

### Image acquisition and pre-processing

MRIs were acquired on a Philips Achieva 3.0T whole-body scanner (Best, The Netherlands) equipped with a 32-channel receive



head coil and MultiTransmit parallel RF transmission. Functional (fMRI) data were acquired using a whole-brain gradient-echo EPI sequence (TR = 2500 ms, TE = 35 ms, slice thickness 3 mm, 40 axial slices, no slice gap, field of view 240 [times] 240 mm<sup>2</sup>, in-plane resolution 3 × 3 mm, SENSE reduction factor 2.0). In addition, high-resolution anatomical images (voxel size = 1 × 1 × 1 mm) were acquired using a standard T1-weighted Three Dimensional Magnetization Prepared Rapid Acquisition Gradient Recalled Echo (3-D MP-RAGE) sequence. Images were analyzed using SPM8 ([www.fil.ion.ucl.ac.uk/spm](http://www.fil.ion.ucl.ac.uk/spm)). Pre-processing consisted of realignment, spatial normalization to the standard EPI template of the Montreal Neurological Institute (MNI) and spatial smoothing using a Gaussian kernel of 6 mm FWHM to meet the statistical requirements of the general linear model (GLM).

### Data analysis

For behavioral analysis, SPSS Statistics 20.0 was used. For each subject, a linear regression was carried out in order to determine the effect of the net expert opinion on change in song desirability. This provided a standardized beta coefficient,  $b_{inf}$ , for each subject representing the degree (in standard deviations) to which the value of songs increased or decreased with expert opinion (Campbell-Meiklejohn et al., 2010). The  $b_{inf}$  beta-coefficient was used as a between-subject regressor for subsequent fMRI analysis.  $b_{inf}$  was normally distributed (Shapiro-Wilk  $W = 0.96$ ,  $P > 0.21$ ).

The fMRI data were analyzed using a GLM as implemented in SPM8. Trials in which subjects chose the unknown rather than the song they provided entered the model as an error regressor of no interest. The experimental conditions (social outcome: agree, disagree and split; non-social outcome: token assigned to preferred song, i.e. 'song won', token assigned to non-preferred song, i.e. 'song not won') were modeled with a duration of 1 s for social outcome or 2 s for non-social outcome and convolved with a canonical hemodynamic response function in the first-level analysis for each subject. Low-frequency signal drifts were filtered using a 128 s high-pass filter. The following contrasts were computed for each participant: (i) agree > disagree (social reward) and (ii) song won > song not won (non-social reward). The individual contrasts were then entered into a second-level group analysis using a between-group two-sample t-test for the comparison between cocaine users and healthy controls and analyzed using small-volume correction (SVC). As the vmPFC has been identified as a key region for the processing of both social and non-social reward (Morelli et al., 2015), it was defined as the main region of interest (ROI). The search volume was a sphere with a 10 mm radius centered on the previously reported peak MNI coordinates 0/58/−6. The search volumes were applied to a two-sample t-test in order to compare cocaine users and healthy controls. Moreover, a previous study (Campbell-Meiklejohn et al., 2012) showed that the tendency to be influenced by expert feedback (captured by  $b_{inf}$ ) correlates with the gray matter volume of the lateral OFC (lOFC). We therefore used the coordinates −33/28/−16 and 36/33/−10 in the lOFC as centers of spherical ROIs (10 mm radius) in order to investigate the correlation between  $b_{inf}$  and brain activation for the social and the non-social reward contrasts. Family-wise error (FWE) corrections were used in all SVC ROI analyses at a peak-level corrected threshold of  $P < 0.05$ . Uncorrected whole-brain results ( $P < 0.001$ ) are shown in Table 2. Correlation analyses (Pearson's product-moment) were conducted to relate  $b_{inf}$  to brain activity.

## Results

### Participant demographics

Healthy controls and cocaine users did not differ significantly with respect to verbal intelligence quotient, years of education, sex distribution, age, smoking status, FTND sum score and the BDI score (Table 1). As intended by our inclusion criteria, cocaine users showed little psychiatric co-morbidities and relatively sparse polytoxic drug use (Table 1).

### Behavioral results

The used paradigm (Figure 1) captured explicit social reward as agreement with knowledgeable others (music experts) and non-social reward as winning a preferred music piece (Campbell-Meiklejohn et al., 2010). Agreement between the subject's and the experts' music preferences constituted social reward. Assignment of the token to the song preferred by the subject, as opposed to the song not preferred by the subject, constituted non-social reward. Social and non-social rewards occurred independently of each other.

Before and after scanning participants rated how much they desired each song. The mean ( $\pm$  standard deviation) song desirability rating was  $7.50 \pm 1.26$  before the experiment and  $7.72 \pm 1.12$  after the experiment. The mean rating of how much the reviewers could be trusted to pick music that the participants would like was  $4.79 \pm 1.36$ . Participants perceived both reviewers as similarly capable of choosing music that the subject would like and there were no group differences in any of the ratings (all  $P > 0.16$ ).

Subjects rated all the songs before and after receiving social feedback through the choice of the experts. For each subject, we quantified how susceptible they were to social influence by the parameter estimate ( $b_{inf}$ ) when regressing the experiment-induced change in song desirability ratings onto net reviewer opinion (Campbell-Meiklejohn et al., 2010). Net reviewer opinion was defined as the difference between the number of times that reviewers preferred the subject's song and the number of times that reviewers preferred the alternative song. On average, healthy controls ( $b_{inf} = 0.05$ ) and cocaine users ( $b_{inf} = -0.05$ ) were similarly influenced by net reviewer opinion [ $T(32) = 1.29$ ,  $P = 0.21$ ]. Moreover, both groups showed similar individual differences in susceptibility to social influence [range of  $b_{inf}$  in healthy controls (max to min): 0.5 to −0.26; in cocaine users: 0.3 to −0.38]. Finally, groups did not differ in their response times during the decision period of the task [ $T(32) = 0.53$ ,  $P = 0.60$ ].

### fMRI results

**Social reward.** First, we tested whether social reward signals induced by agreement with experts differed between healthy controls and cocaine users. Based on its involvement in social and non-social reward processing (Morelli et al., 2015), we performed this analysis within the vmPFC (with SVC; for whole-brain results see Table 2). Specifically, we compared brain responses during agreement vs disagreement with the experts in a vmPFC region previously implicated in processing both social and non-social reward value in healthy controls (Morelli et al., 2015). The vmPFC region showed a significant group difference for this type of social reward, such that social reward responses were stronger in healthy controls than cocaine users (Figure 2A and B). These findings suggest that blunting of vmPFC responding occurs for the explicit social reward of agreeing with an expert about music.

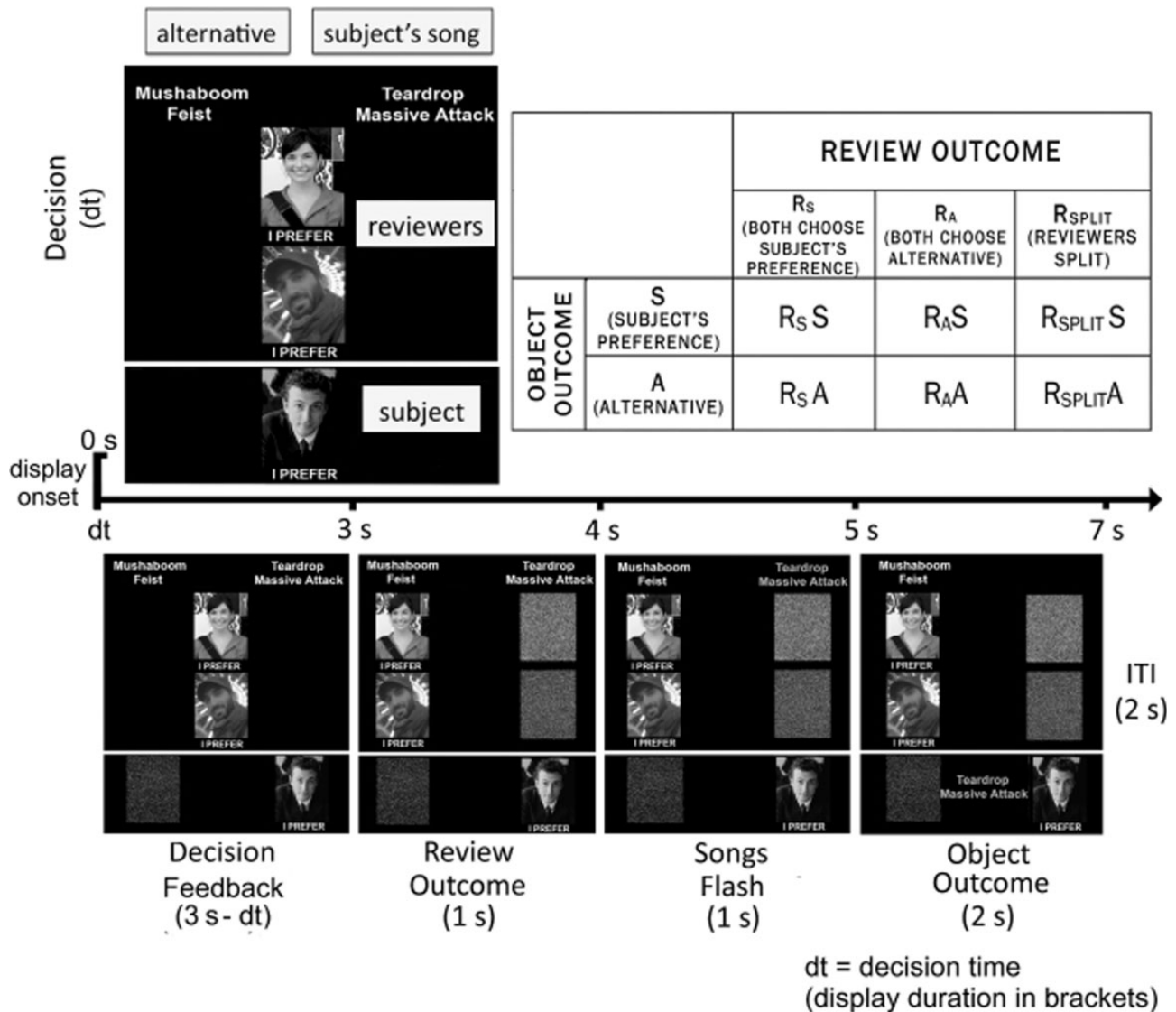


Fig. 1. Task display and trial structure (reprinted from Campbell-Meiklejohn et al., 2010). The critical contrasts concerned trials in which both experts agreed vs disagreed with the participant (social reward) and trials in which the participant won their preferred song vs the alternative song (non-social reward). Depicted here is a disagreement trial (absence of social reward) in which the preferred song was won (presence of non-social reward). Social and non-social rewards occurred independently of each other.

**Non-social reward.** To test whether the vmPFC would show altered non-social reward processing in cocaine users, we compared responses across experimental groups when the preferred song was won as opposed to when the preferred song was not won. The same vmPFC region (McClure et al., 2004) also showed a significant group difference for tokens assigned to preferred vs non-preferred songs, such that non-social reward responses were stronger in healthy controls than cocaine users (for SVC results see Figure 3A and B; for whole-brain results see Table 2).

**Overlap of social and non-social reward differences.** To test whether vmPFC blunting coincided for social and non-social reward, we next tested for overlap. As already suggested by the close proximity of the respective activation maps (Figures 1A and 2A), using either an inclusive masking approach or a conjunction, we found indeed overlap of seven voxels with both types of differential reward activations in the vmPFC (Figure 3C). These data indicate that a blunted response of the vmPFC

forms a common path for a general deficit in non-drug-related reward valuation in cocaine users.

**Relation of social reward responses to social influence.** A previous study found a positive association between the degree to which expert feedback influenced song desirability and thickness of the LOFC in healthy volunteers (Campbell-Meiklejohn et al., 2012). We therefore tested whether the relation between social reward signals and the propensity to be influenced by social feedback (as captured by the  $b_{inf}$  parameter) was more positive in the LOFC of healthy controls than in the LOFC of cocaine users. Testing for differences between groups in their correlation of brain activation during social reward (as captured by the first eigenvariate of the contrast agree > disagree) with  $b_{inf}$ , we found that both indeed significantly differed (Figure 4A). As predicted, the relation between social reward responses and the propensity to be influenced by expert feedback was positive in healthy controls (Figure 4B;  $r = 0.559$ ,  $P = 0.02$ ). In contrast, this relation was reverted in cocaine users ( $r = -0.619$ ,  $P = 0.008$ ) and

Table 2. Whole-brain analyses

Brain region	Hemisphere	k	T	x	y	z
Agree > disagree						
Calcarine Sulcus	L	49	4.34	4	-92	6
<b>Ventromedial prefrontal cortex</b>	<b>L</b>	<b>55</b>	<b>4.12</b>	<b>-8</b>	<b>56</b>	<b>-4</b>
Middle temporal gyrus	L	13	4.27	-60	-54	2
Middle temporal gyrus	L	5	4.06	-56	-46	0
Middle temporal gyrus	L	23	4.02	-54	-34	-2
Middle temporal gyrus	L	5	3.97	-50	-74	20
Middle temporal gyrus	L	4	3.96	-52	2	-26
Inferior parietal lobule	L	15	3.94	-46	-46	46
Hippocampus	L	8	3.92	-26	-6	-20
Superior frontal gyrus	R	7	3.89	18	-4	56
Postcentral gyrus	R	6	3.82	58	-18	40
Superior temporal gyrus	R	13	3.79	62	-46	18
Middle frontal gyrus	L	4	3.78	-36	38	34
Middle temporal gyrus	L	4	3.78	-62	-34	0
Middle frontal gyrus	R	5	3.75	32	4	60
Inferior parietal lobule	R	5	3.69	54	-54	44
Inferior parietal lobule	L	4	3.67	-50	-50	42
Middle temporal gyrus	L	3	3.65	-64	-16	-2
Insula	R	5	3.62	40	-10	20
Insula	L	8	3.59	-38	16	2
Superior frontal gyrus	R	6	3.54	28	4	62
Pref. song won > pref. song not won						
Cerebellum	L	123	5.77	-8	-54	-28
Posterior cingulate cortex	R	633	5.06	12	-54	16
Cerebellum	R	901	4.78	16	-52	-6
Insula	L	58	4.16	-28	-32	12
Middle temporal gyrus	L	19	3.89	-50	-70	22
Lingual gyrus	R	14	3.86	14	-72	0
<b>Ventromedial prefrontal cortex</b>	<b>L</b>	<b>42</b>	<b>3.49</b>	<b>-6</b>	<b>62</b>	<b>0</b>
<b>Lateral orbitofrontal cortex</b>	<b>L</b>	<b>5</b>	<b>3.79</b>	<b>-28</b>	<b>30</b>	<b>-14</b>
Precentral gyrus	L	5	3.71	-38	-8	54
Cerebellum	R	29	3.69	14	-48	-26
Middle cingulate cortex	R	4	3.64	14	-36	30
Lingual gyrus	L	3	3.61	-22	-72	2
Lingual gyrus	L	6	3.61	-20	-60	-6
Middle temporal gyrus	R	7	3.60	42	-58	18
Thalamus	R	13	3.54	2	-22	4
Fusiform gyrus	L	4	3.48	-30	-44	-16
Correlation agree > disagree-Binf						
Lingual gyrus	R	118	4.81	14	-62	-4
<b>Lateral orbitofrontal cortex</b>	<b>L</b>	<b>13</b>	<b>4.38</b>	<b>-30</b>	<b>20</b>	<b>-22</b>

Differences between groups (healthy controls > cocaine users) for the contrasts agree > disagree (social reward), song won > song not won (non-social reward) and correlation between agree > disagree and Binf. Statistical threshold:  $P < 0.001$  (uncorrected),  $k > 2$ ; significant activations after small volume FWE correction ( $P < 0.05$ ) are displayed in bold; all activations represent the group contrast controls > cocaine users.

no group differences in correlations arose for the vmPFC (for SVC results see Figure 4; for whole-brain results see Table 2). Moreover, there was no relation between the  $b_{\text{inf}}$  parameter and non-social reward in either group (controls:  $r = 0.01$ ,  $P > 0.97$ ; cocaine users:  $r = 0.11$ ,  $P > 0.67$ ). Thus, cocaine users appear to relate social reward signals to social influence differently from healthy controls and this effect appears to be relatively specific for IOFC and social reward.

## Discussion

Here, we demonstrate that the brain responses of chronic cocaine users differ from those of healthy control subjects for non-drug-related rewards. Thus, blunting of vmPFC responses is not specific to social or non-social reward. On the other hand, our IOFC results suggest that cocaine users show specific changes in social reward processing and in how the propensity to follow social feedback impacts social reward responses.

Our finding of a significant group difference in the impact of expert feedback on IOFC responses to being in agreement with the experts (Figure 4) demonstrates that social reward processing is altered in cocaine users and extend previous reports of deficits in social cognition and social interaction in cocaine users (Fox et al., 2007, 2011; Hulka et al., 2013, 2014; Preller et al., 2014b). These results are also in line with studies in non-human primates showing that social factors such as group hierarchy interact with dopamine D2-mediated vulnerability to cocaine use (Morgan et al., 2002).

Compared with healthy controls, cocaine users showed significantly less activation of the vmPFC in response to both agreement vs disagreement with music experts and winning vs losing a preferred song. These findings may suggest a generalized blunting of neural responses to rewards that are not drug-related and contrast with previous findings of enhanced vmPFC activity in cocaine users in response to drug-related words indicating increased reward valuation for drug cues (Kufahl et al., 2008; Smith et al., 2014). The two strands of research find one common explanation in the notion that the vmPFC is involved in the attribution of personal relevance (or subjective value) to environmental stimuli and behavioral responses (for comparison of different reward types see Sescousse et al., 2013b; for review Moeller and Goldstein, 2014). In the course of cocaine addiction, the subjective value of drug-related rewards increases, whereas the personal relevance of non-drug-related rewards becomes reduced. The present activation pattern of generalized blunting of both non-social and social non-drug-related reward processing by the vmPFC of cocaine users appears to follow exactly this scheme.

Experimental cocaine administration has been shown to deteriorate OFC functions in rodents (Lucantonio et al., 2012) and non-human primates (Olausson et al., 2007). Such findings support the assumption that neuroadaptations in brain reward systems make drug users more sensitive to the abused drug, while their reduced responsiveness to the value of non-drug reinforcers may discourage them from giving up drug use in the long term (Volkow et al., 2011). Specifically, drug use-related metabolic changes in vmPFC and OFC seem to be mediated by changes in striatal dopamine D2 receptor density (Volkow et al., 1993). Consequently, the here shown changes in reward processing of cocaine users might be drug induced rather than pre-disposed. However, this hypothesis has to be tested in a longitudinal study design in the future.

Given that the vmPFC appears to serve as a common hub for various types of reward, including drug reward, it appears unlikely that unspecific treatments, such as a pharmacological substance will facilitate recovery. In contrast, our data suggest that a psychotherapy addressing social reward processing may be more promising, also in light of the fact that the IOFC and the vmPFC are mutually connected and that this connection seems to be reduced compared with healthy controls in other forms of addiction (Ma et al., 2010). Psychotherapy could enhance sensitivity to social rewards. As a consequence, the preferential



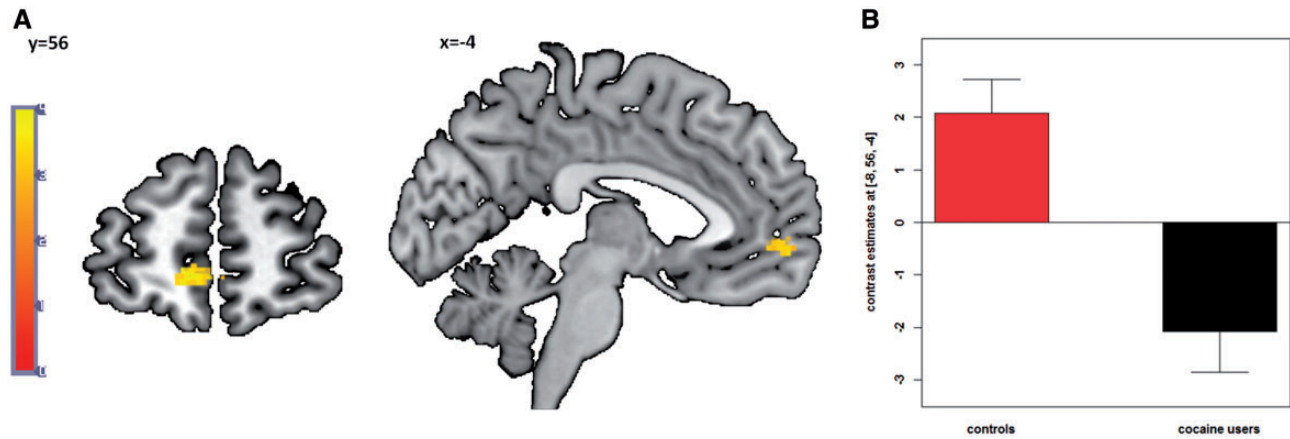


Fig. 2. Social reward blunting in vmPFC of cocaine users. (A) Between-group activation [controls ( $n = 17$ ) > cocaine users ( $n = 17$ )] for the contrast agree > disagree (displayed at  $P < 0.005$ ; SVC based on social reward vmPFC region described in Morelli et al., 2015; peak at  $x/y/z = -8/56/-4$ ;  $T = 4.12$ ). (B) Contrast estimates for the vmPFC peak illustrated in A. Error bars refer to standard error of contrast estimates.

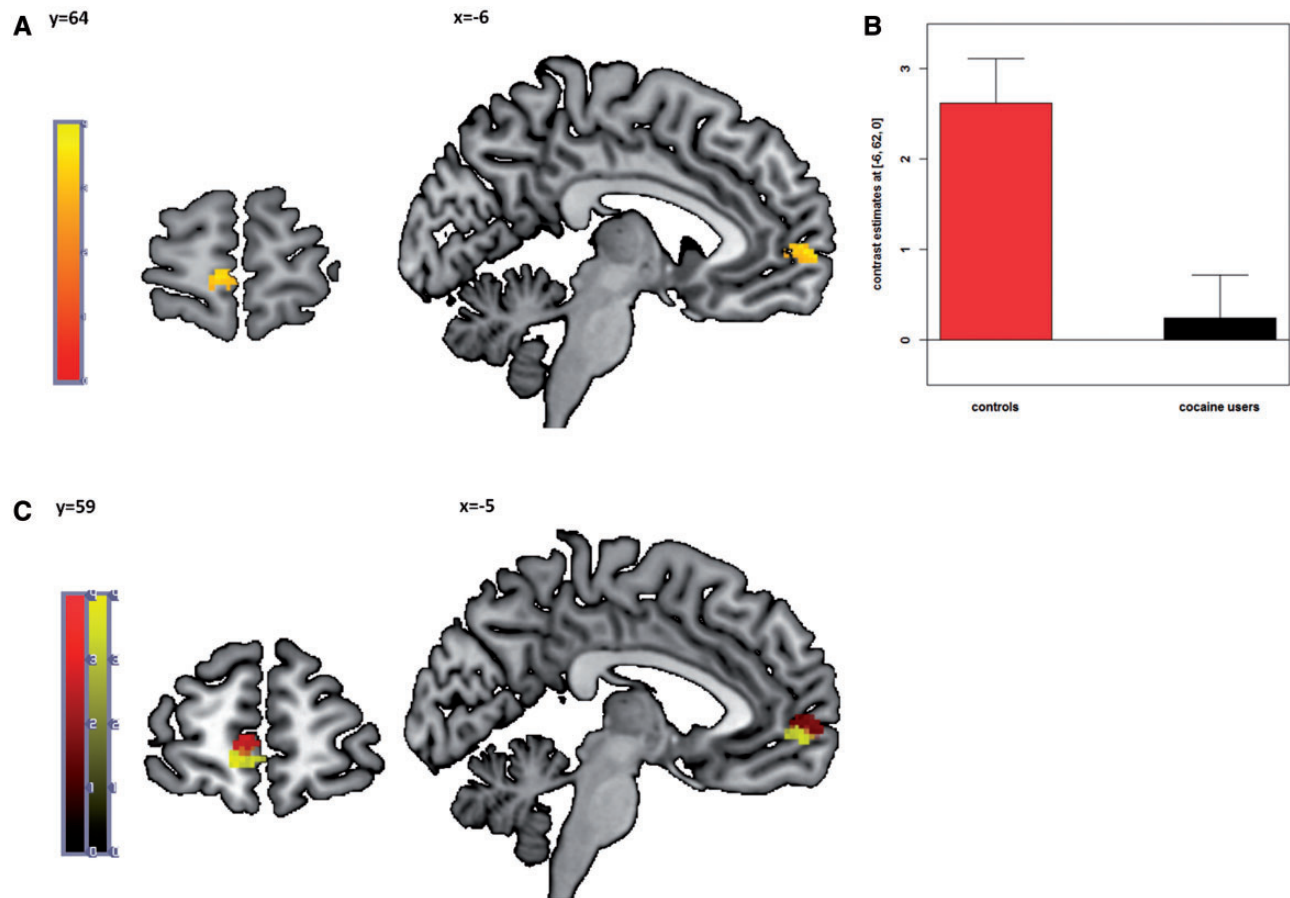


Fig. 3. Non-social reward blunting in vmPFC of cocaine users. (A) Between-group activation [controls ( $n = 17$ ) > cocaine users ( $n = 17$ )] for the contrast song won > song not won (displayed at  $P < 0.005$ ; SVC based on a social and non-social reward vmPFC region described in Morelli et al., 2015; peak at  $x/y/z = -6/62/0$ ;  $T = 3.49$ ). (B) Contrast estimates for the vmPFC peak illustrated in A. (C) Overlapping activation (orange) of social reward (agree > disagree; yellow) and non-social reward (song won > song not won; red) contrast in the vmPFC. Error bars refer to standard error of contrast estimates.

processing of drug-related rewards might be diminished, both at the behavioral and the neural level.

The present study has to be interpreted with the following limitations in mind: (i) The sample size was modest. However, cocaine users were relatively free of psychiatric comorbidity

and showed no polytoxic drug-use pattern. (ii) Following the original design of Campbell-Meiklejohn et al. (2010), we did not jitter the intertrial interval or the interval between social and non-social outcomes. However, note that the two outcome types were entirely independent of each other, which makes jittering



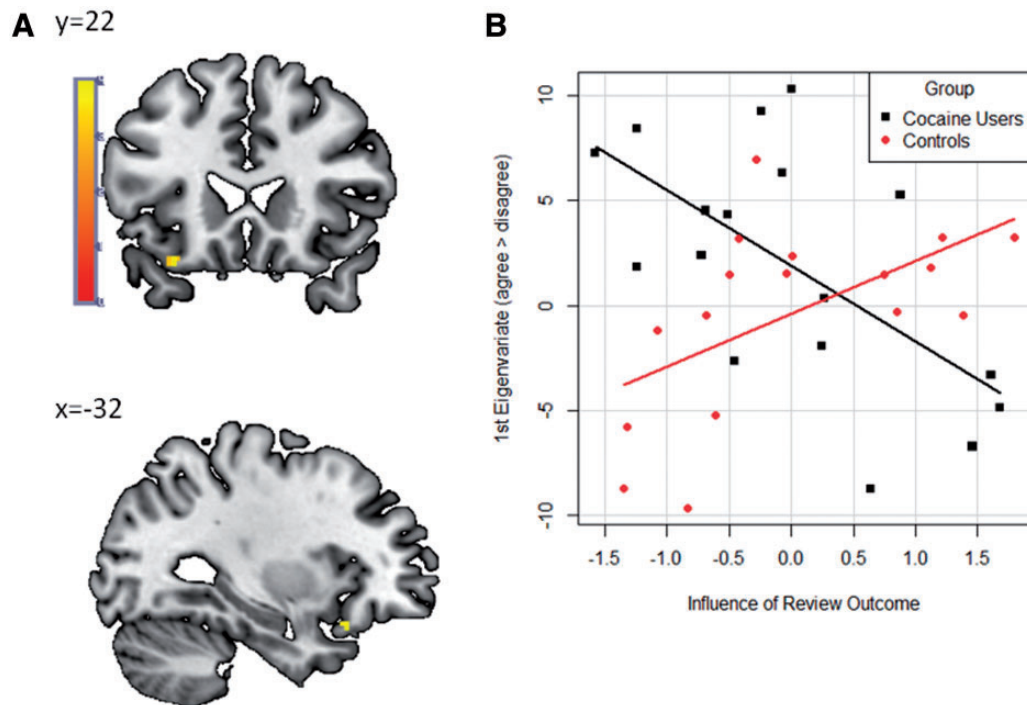


Fig. 4. Differential effect of social feedback on social reward signals in IOFC. (A) Between-group difference [controls ( $n = 17$ ) > cocaine users ( $n = 17$ )] for the correlation between the contrast agree > disagree and the social influence ( $b_{int}$ ) of expert decisions on later song ratings (displayed at  $P < 0.005$ ; SVC based on IOFC region described in Campbell-Meiklejohn et al., 2012; peak at  $x/y/z = -32/22/-22$ ;  $T = 4.09$ ). (B) Scatterplot illustrating the effect shown in A.

less necessary. (iii) It should be kept in mind that there are different definitions of social reward, some with very little personal relevance (e.g. Seid-Fatemi and Tobler, 2015), others providing value more directly, such as praise. Depending on the degree of personal relevance (Moeller and Goldstein, 2014), distinct forms of reward appear to activate dorsal or ventral parts of MPFC (Seid-Fatemi and Tobler, 2015) and it remains to be seen whether forms of social reward with less personal relevance are also blunted in cocaine users. The degree of personal relevance (or individual reward value) of social reward might arise also for the ventral striatum, which is more active for non-social than social reward (Morelli et al., 2015). (iv) More generally, although social reward processing represents an elegant tool to investigate basic social functions, it cannot cover all facets of social interaction behavior. (v) Due to the cross-sectional design, we cannot exclude that the blunting of social reward processing has preceded cocaine use and possibly represents a vulnerability to start using drugs.

In sum, our study shows a generalized blunting of reward processing in the vmPFC of cocaine users. Moreover, we demonstrate that activity in the IOFC to social reward is differently affected by social feedback in cocaine compared with stimulant-naïve controls. Understanding the basis of social reward deficits in stimulant users offers the possibility to develop new targets for prevention and treatment strategies. Ideally, remediation of social reward by psychotherapy and training interventions would result in providing a counterpoint to the exaggerated drug-related reward signals in substance use disorders and in restoring non-drug-related reward signals.

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## References

- Beck, A.T., Ward, C.H., Mendelson, M., Mock, J., Erbaugh, J. (1961). An inventory for measuring depression. *Archives of General Psychiatry*, 4, 561–71.
- Bhanji, J.P., Delgado, M.R. (2014). The social brain and reward: Social information processing in the human striatum. *Wiley Interdisciplinary Reviews: Cognitive Science*, 5(1), 61–73.
- Burke, C.J., Tobler, P.N., Schultz, W., Baddeley, M. (2010). Striatal BOLD response reflects the impact of herd information on financial decisions. *Frontiers of Human Neuroscience*, 4, 48.
- Campbell-Meiklejohn, D.K., Bach, D.R., Roepstorff, A., Dolan, R.J., Frith, C.D. (2010). How the opinion of others affects our valuation of objects. *Current Biology*, 20(13), 1165–70.
- Campbell-Meiklejohn, D.K., Kanai, R., Bahrami, B., Bach, D.R., Dolan, R.J., Roepstorff, A., et al. (2012). Structure of orbitofrontal cortex predicts social influence. *Current Biology*, 22(4), R123–4.
- Degenhardt, L., Hall, W. (2012). Extent of illicit drug use and dependence, and their contribution to the global burden of disease. *Lancet*, 379(9810), 55–70.
- Ersche, K.D., Barnes, A., Jones, P.S., Morein-Zamir, S., Robbins, T.W., Bullmore, E.T. (2011). Abnormal structure of frontostriatal brain systems is associated with aspects of impulsivity and compulsivity in cocaine dependence. *Brain*, 134(Pt 7), 2013–24.
- Ersche, K.D., Williams, G.B., Robbins, T.W., Bullmore, E.T. (2013). Meta-analysis of structural brain abnormalities associated with

- stimulant drug dependence and neuroimaging of addiction vulnerability and resilience. *Current Opinion in Neurobiology*, **23**(4), 615–24.
- Fox, H.C., Axelrod, S.R., Paliwal, P., Sleeper, J., Sinha, R. (2007). Difficulties in emotion regulation and impulse control during cocaine abstinence. *Drug and Alcohol Dependence*, **89**(2–3), 298–301.
- Fox, H.C., Bergquist, K.L., Casey, J., Hong, K.A., Sinha, R. (2011). Selective cocaine-related difficulties in emotional intelligence: Relationship to stress and impulse control. *The American Journal of Addiction*, **20**(2), 151–60.
- Franklin, T.R., Acton, P.D., Maldjian, J.A., et al. (2002). Decreased gray matter concentration in the insular, orbitofrontal, cingulate, and temporal cortices of cocaine patients. *Biological Psychiatry*, **51**(2), 134–42.
- Goldstein, R.Z., Alia-Klein, N., Tomasi, D., et al. (2007a). Is decreased prefrontal cortical sensitivity to monetary reward associated with impaired motivation and self-control in cocaine addiction? *The American Journal of Psychiatry*, **164**(1), 43–51.
- Goldstein, R.Z., Tomasi, D., Alia-Klein, N., et al. (2007b). Subjective sensitivity to monetary gradients is associated with frontolimbic activation to reward in cocaine abusers. *Drug and Alcohol Dependence*, **87**(2–3), 233–40.
- Heatherton, T.F., Kozlowski, L.T., Frecker, R.C., Fagerstrom, K.O. (1991). The Fagerstrom test for nicotine dependence: A revision of the Fagerstrom Tolerance Questionnaire. *British Journal of Addiction*, **86**(9), 1119–27.
- Howard, J.D., Gottfried, J.A., Tobler, P.N., Kahnt, T. (2015). Identity-specific coding of future rewards in the human orbitofrontal cortex. *Proceedings of the National Academy of Sciences of the United States of America*, **112**(16), 5195–200.
- Hulka, L.M., Eisenegger, C., Preller, K.H., et al. (2014). Altered social and non-social decision-making in recreational and dependent cocaine users. *Psychological Medicine*, **44**(5), 1015–28.
- Hulka, L.M., Preller, K.H., Vonmoos, M., Broicher, S.D., Quednow, B.B. (2013). Cocaine users manifest impaired cross-modal emotion processing. *Frontiers in Psychiatry*, **4**, 98.
- Jia, Z., Worhunsky, P.D., Carroll, K.M., et al. (2011). An initial study of neural responses to monetary incentives as related to treatment outcome in cocaine dependence. *Biological Psychiatry*, **70**(6), 553–60.
- Klucharev, V., Hytonen, K., Rijpkema, M., Smidts, A., Fernandez, G. (2009). Reinforcement learning signal predicts social conformity. *Neuron*, **61**(1), 140–51.
- Kufahl, P., Li, Z., Risinger, R., et al. (2008). Expectation modulates human brain responses to acute cocaine: A functional magnetic resonance imaging study. *Biological Psychiatry*, **63**(2), 222–30.
- Lehrl, S. (1999). *Mehrfachwahl-Wortschatz-Intelligenztest (MWT-B)*. Göttingen, Germany: Hogrefe.
- Lucantonio, F., Stalnaker, T.A., Shaham, Y., Niv, Y., Schoenbaum, G. (2012). The impact of orbitofrontal dysfunction on cocaine addiction. *Nature Neuroscience*, **15**(3), 358–66.
- Ma, N., Liu, Y., Li, N., et al. (2010). Addiction related alteration in resting-state brain connectivity. *NeuroImage*, **49**(1), 738–44.
- McClure, S.M., Laibson, D.I., Loewenstein, G., Cohen, J.D. (2004). Separate neural systems value immediate and delayed monetary rewards. *Science*, **306**(5695), 503–7.
- Moeller, S.J., Goldstein, R.Z. (2014). Impaired self-awareness in human addiction: Deficient attribution of personal relevance. *Trends in Cognitive Science*, **18**(12), 635–41.
- Morelli, S.A., Sacchet, M.D., Zaki, J. (2015). Common and distinct neural correlates of personal and vicarious reward: A quantitative meta-analysis. *NeuroImage*, **112**, 244–53.
- Morgan, D., Grant, K.A., Gage, H.D., et al. (2002). Social dominance in monkeys: Dopamine D2 receptors and cocaine self-administration. *Nature Neuroscience*, **5**(2), 169–74.
- Olausson, P., Jentsch, J.D., Krueger, D.D., Tronson, N.C., Nairn, A.C., Taylor, J.R. (2007). Orbitofrontal cortex and cognitive-motivational impairments in psychostimulant addiction: Evidence from experiments in the non-human primate. *Annals of the New York Academy of Science*, **1121**, 610–38.
- Oldfield, R.C. (1971). The assessment and analysis of handedness: The Edinburgh inventory. *Neuropsychologia*, **9**(1), 97–113.
- Patel, K.T., Stevens, M.C., Meda, S.A., et al. (2013). Robust changes in reward circuitry during reward loss in current and former cocaine users during performance of a monetary incentive delay task. *Biological Psychiatry*, **74**(7), 529–37.
- Preller, K.H., Herdener, M., Schilbach, L., et al. (2014a). Functional changes of the reward system underlie blunted response to social gaze in cocaine users. *Proceedings of the National Academy of Sciences of the United States of America*, **111**(7), 2842–7.
- Preller, K.H., Hulka, L.M., Vonmoos, M., et al. (2014b). Impaired emotional empathy and related social network deficits in cocaine users. *Addiction Biology*, **19**(3), 452–66.
- Preller, K.H., Ingold, N., Hulka, L.M., et al. (2013). Increased sensorimotor gating in recreational and dependent cocaine users is modulated by craving and attention-deficit/hyperactivity disorder symptoms. *Biological Psychiatry*, **73**(3), 225–34.
- Quednow, B.B., Kuhn, K.U., Hoenig, K., Maier, W., Wagner, M. (2004). Prepulse inhibition and habituation of acoustic startle response in male MDMA (“Ecstasy”) users, cannabis users, and healthy controls. *Neuropsychopharmacology*, **29**(5), 982–90.
- Seid-Fatemi, A., Tobler, P.N. (2015). Efficient learning mechanisms hold in the social domain and are implemented in the medial prefrontal cortex. *Social Cognitive and Affective Neuroscience*, **10**(5), 735–43.
- Sescousse, G., Barbalat, G., Domenech, P., Dreher, J.C. (2013a). Imbalance in the sensitivity to different types of rewards in pathological gambling. *Brain*, **136**(Pt 8), 2527–38.
- Sescousse, G., Caldu, X., Segura, B., Dreher, J.C. (2013b). Processing of primary and secondary rewards: A quantitative meta-analysis and review of human functional neuroimaging studies. *Neuroscience & Biobehavioral Reviews*, **37**(4), 681–96.
- Smith, D.G., Simon Jones, P., Bullmore, E.T., Robbins, T.W., Ersche, K.D. (2014). Enhanced orbitofrontal cortex function and lack of attentional bias to cocaine cues in recreational stimulant users. *Biological Psychiatry*, **75**(2), 124–31.
- Tiffany, S.T., Singleton, E., Haertzen, C.A., Henningfield, J.E. (1993). The development of a cocaine craving questionnaire. *Drug and Alcohol Dependence*, **34**(1), 19–28.
- Volkow, N.D., Baler, R.D., Goldstein, R.Z. (2011). Addiction: Pulling at the neural threads of social behaviors. *Neuron*, **69**(4), 599–602.
- Volkow, N.D., Fowler, J.S., Wang, G.J., et al. (1993). Decreased dopamine D2 receptor availability is associated with reduced frontal metabolism in cocaine abusers. *Synapse*, **14**(2), 169–77.
- Vonmoos, M., Hulka, L.M., Preller, K.H., et al. (2013). Cognitive dysfunctions in recreational and dependent cocaine users: Role of attention-deficit hyperactivity disorder, craving and early age at onset. *British Journal of Psychiatry*, **203**, 35–43.